Colloid osmotic pressure: its measurement and clinical value

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Plasma colloid osmotic pressure (COP) is an important determinant in the appearance of edema. The development of a simple technique for COP measurement, based on an electronic pressure transducer and a semipermeable membrane system, has led to an appreciation of the value of COP determinations in clinical practice. In a steady state the measured COP replicates the value computed from serum proteins. In pathologic sera a derived value is unreliable. The normal human plasma COP averages 25.4 mm Hg. This value tends to decrease with age, is lower in females and is also lower in subjects at bed rest. As a clinical tool COP measurement represents an unduplicated contribution to the differential diagnosis of pulmonary edema. In critically ill patients COP measurement represents a reliable predictor of survival.

La pression colloïdale osmotique (PCO) est un déterminant important dans l'apparition de l'oedème. La mise au point d'une technique simple de mesure de la PCO, qui repose sur l'utilisation d'un transducteur de pression électronique et sur un système de membrane semiperméable, a mené à une appréciation de la valeur clinique de la mesure de la PCO. A l'état stable, les mesures de la PCO coincident avec les valeurs calculées à partir des protéines sériques. Dans les cas pathologiques, les valeurs dérivées ne sont pas fiables. La PCO du plasma humain normal est en moyenne de 25.4 mm Hg. Cette valeur tend à diminuer avec l'âge, et elle est plus faible chez la femme et, aussi, chez les sujets alités. En clinique, la mesure de la PCO constitue un apport sans équivalent au diagnostic différentiel de l'oedème pulmonaire. Chez les malades en phase critique, la mesure de la PCO représente un indice sûr de prédiction de la survie.

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Starling,[1] 80 years ago, suggested that intravascular colloids promote fluid absorption from the interstitial space at the microcirculatory level. Subsequently Guyton and Lindsey[2] presented quantitative evidence to substantiate the importance of the relation between left atrial pressure and plasma protein concentration in the development of pulmonary edema.

Colloid osmotic pressure (COP) was first suspected[3] and later clinically implicated[4,5] as an important determinant in the development of systemic and pulmonary edema in clinical situations. The relevance of its direct measurement as a bedside guide has now become appreciated.

This review is based on the information available throughout the literature, and fundamental and clinical information collected in collaboration with my colleagues.

Measurement

Principle

The delay between the growth of knowledge based on research into COP and its clinical application resulted mainly from the absence of a simple and reliable method of measurement. Because of a wide margin of uncertainty in individual cases the indirect methods cannot be considered as exact.[6-10] With the introduction of the electronic pressure transducer[11,12] for measurement of COP, however, serial measurements of small samples became possible, and modifications of the original design further improved the technique.[10,13-18]

The basic principle underlying measurement of COP is separation of two chambers of fluid by a semipermeable membrane. The chamber below the membrane is filled with a colloid-free isotonic saline solution and connected to the pressure transducer. The upper face of the membrane represents the base of the second chamber, which is filled with the sample to be measured. The membrane selected must be freely permeable to small molecules but impermeable to large molecules. A zero reference level is obtained by placing isotonic saline solution in the sample chamber. When an unknown solution is placed in the sample chamber the colloid osmotic force created at the membrane causes fluid to move from the lower chamber to the sample chamber, creating a negative pressure in the transducer chamber. This pressure equals the COP of the unknown solution.

Choice of standard and sample

The progress accomplished during the last 10 years concerning the role of COP in human physiology and pathology is largely the consequence of the original work of Hansen.[11,13]

A relative limitation of the technique of measurement is the need for a calibrating standard for quantitation of the membrane.[19] Because a stable standard commercial solution is so far unavailable, a reference solution of 5% human albumin or 3% dextran 70 is generally chosen.

The blood to be analysed may be drawn from either an artery or a central vein. The slight difference in COP attributable to differences in pH does not lead to significant differences in results.[10,20] If a peripheral vein is chosen as the sampling site stasis from the use of a tourniquet should be avoided, as a significant increase in venous pressure will secondarily increase the mean capillary microvascular pressure. Water then will be filtered from the blood and the COP will be artifactually increased.[20]

Depending on the specifications of the instrument the volume of a sample may vary from 0.5 ml to 1 μl. The time required for a single measurement is longer for smaller samples and varies from 1.5 to 15 minutes. The reproducibility of duplicate measurement is inversely proportional to the size of the sample; the value is reproducible within 0.15 mm Hg in large samples and 0.7 mm Hg in the smallest.

The osmotic pressure generated by the fibrinogen in plasma represents a relatively small fraction of the total COP; therefore, the COP in plasma is about 0.35 mm Hg greater than the COP in serum — a difference that is statistically significant ($P < 0.0025$).[20] To preserve this protein whole blood should be anticoagulated. Dried heparin is the most reliable anticoagulant;[21] its concentration should not exceed 200 U/ml.[10]

Free hemoglobin in plasma also generates osmotic pressure that increases the measured COP.[20] Hemolysis during sampling or processing should be avoided. Samples of plasma but not of whole blood can be refrigerated for periods of 1 to 7 days before processing without affecting the measurement of COP.[20] Freezing the specimen is best avoided.

Physiologic variations of COP

The COP is determined mainly by the concentration of protein in plasma: 1 g of protein retains about 15 ml of solution in the vascular space.[22] In a steady state, at physiologic pH, the COP can reasonably be derived from van't Hoff's theory and the Donnan effect.[23] The function used in giving the relation of the albumin curve to COP is represented by a parabola and that for globulin, by a straight line.[2,23] Any major departure from a steady state or an abnormal physiologic condition alters the reliability of the calculated COP, the variation being particularly great in pathologic sera. This inaccuracy is the result of the lack of proportional changes in protein and salts, the greater heterogeneity of the globulins and the interaction between the proteins.[6,13,19,23] The unreliability of a derived value is sufficient to make it necessary to determine the plasma COP directly in any situation in which this parameter is considered to be important.[6-8,13,24]

Data relating to the variation of COP due to age and sex have been reported for small groups[7,25] with conflicting results. Analysis of samples from a large population reveals a gradual but progressive and significant ($P < 0.005$) decrease of COP with age. COP is also slightly but significantly ($P < 0.005$) lower in women. These data are summarized in Table I.

A significantly lower COP is detected in patients who have been supine for several hours compared with ambulatory subjects.[7,10,20,25,26] COP is 15% lower in subjects at bed rest than in a normal ambulatory population (Table II). The increase in plasma COP in ambulatory subjects is thought to be secondary to the reduction in plasma volume associated with exercise;[7,27] any interpretation extrapolated from a normal ambulatory population to bedridden patients should therefore be avoided. This important consideration is often neglected.

Repetitive measurements of COP in the same subject over a period of 12 weeks have disclosed a fluctuation of up to 10%, which is a significant ($P < 0.01$) variation.[7,20]

Values for COP and mean systemic arterial pressure are correlated ($r = 0.50$).[19,25] For each increase in blood pressure of 10 mm Hg an increase in COP of 0.75 mm Hg may be expected. This suggests that a relative concomitant increase in the mean microvascular pressure parallels the increase in the systemic blood pressure, the former promoting fluid exchanges at the capillary level. No correlation was found between COP and hematocrit values.[19,24]

Within the limits of variation of pH compatible with survival no correlation was detected between COP and pH (Table III).

At comparable concentrations dextrans exert an osmotic pressure that is two to eight times greater than the oncotic pressure of plasma proteins.[28] Gram for gram the dextran tends to attract intravascularly about 45% more interstitial fluid than the plasma protein.[29]

The variations of COP during fetal life are of interest in relation to fetal–maternal fluid exchange. At midterm the COP in fetal sheep is about 8.5 mm Hg.[30] It gradually increases during gestation but never exceeds that of the maternal blood.

The interspecies variation of COP was studied by Meyer[31] and Zweifach and Intaglietta.[24] COP varies in mammals from 10.0 mm Hg (Himalayan goats) to 27.0 mm Hg (dolphins). This is in part determined by the correlation that exists between blood pressure and COP.

COP in pathologic states

The role of COP in the pathophysiology of disease is largely unexplored. Following the efforts of Starling[1] and Guyton and Lindsey,[2] many other clinical investigators have tried to alter the COP–left ventricular filling pressure gradient and, by doing so, to restore the intravascular blood volume or reverse interstitial fluid loss.

One means of reversing the gradient for fluid exchanges in favour of the intravascular compartment is to increase the plasma COP by infusing albumin. A few successful clinical trials have been reported.[32,33] In attempts to correct acute respiratory failure in critically ill patients albumin infusions alone accounted for some improvement in 40% of the patients; the addition of a potent diuretic (furosemide or

Table I—Variation in colloid osmotic pressure (COP) with age and sex*

Variable	COP (mm Hg) Mean ± SD
Age (yr)	
< 50	21.1 ± 4.7†
50 – 70	20.7 ± 4.2
70 – 89	19.7 ± 3.7†
Sex	
Male	21.6 ± 4.8†
Female	19.6 ± 4.2†

*Determinations based on values for 100 supine patients in each age group.
†Difference significant, $P < 0.005$.

Table II—COP in normal subjects, ambulatory and supine

Condition	COP (mm Hg) Mean ± SD
Ambulatory (n = 19)	25.4 ± 2.3*
Supine (n = 14)	21.6 ± 3.6*

*Difference significant, $P < 0.005$.

Table III—COP and pH

Determination*	COP (mm Hg)	pH
Highest	33.9	7.61
Lowest	11.6	7.04
Mean	19.2 ± 3.8	7.40 ± 0.09
r	0.044	

*Based on 100 determinations.

ethacrynic acid) to the albumin infusion succeeded in improving the alveolar–arterial oxygen gradient in about 70% of the patients. The extent of improvement is correlated with the volume diuresed. Improvement in gas exchange was thought to be secondary to the restoration of a normal COP coupled with the removal of excess fluid from the lung interstitium.

The relatively poor success of attempts to correct respiratory failure with albumin infusion alone represents a first warning against an oversimplified application of the traditional Starling[1] hypothesis to the clinical situation. The first conclusion is that the theory still holds in a relatively small proportion of critically ill patients. The failure rate is otherwise significant, and even paradoxical deterioration of the patient may be observed after the administration of albumin.[32] The increase in blood volume may be far less than expected.[34] The COP may continue to decrease despite the administration of albumin.[35] The quality of the microvascular exchange membranes has to be considered.[36,37] Massive transcapillary escape of albumin may follow its infusion, preventing any appreciable increase in plasma volume, and the total interstitial water content may then increase instead of decrease through reabsorption.[38]

Adding direct COP measurement to estimation of the capillary pulmonary artery wedge pressure permits bedside evaluation of the type of pulmonary edema in evolution, allowing a more specific planning of treatment.[39]

Even if left ventricular failure is the most common cause of clinical pulmonary edema other causes have to be considered, whatever the age of the patient and primary diagnosis.[40]

A dynamic relation between COP and left ventricular filling pressure has been reported in dogs.[2,41,42] The filling pressure in the left ventricle at which pulmonary edema starts to appear was shown to vary in direct proportion to COP.[2] Nevertheless the proposed critical range of pulmonary artery wedge pressure for appearance of alveolar pulmonary edema was considered, until very recently, to lie between 23 and 25 mm Hg.[43] Pulmonary edema has, however, been reported to occur at a much lower left ventricular filling pressure after acute myocardial infarction in man.[44]

If COP and pulmonary artery wedge pressures are measured simultaneously at the time of appearance of pulmonary edema, this event becomes predictable.[45] In patients with an acute myocardial infarction pulmonary edema may appear in the absence of an increase in the left ventricular filling pressure if the COP is low and the gradient for fluid exchanges almost abolished. In the absence of pulmonary edema the gradient averaged 10 mm Hg; in patients with pulmonary edema it was reduced to 1 mm Hg.[45]

Measurement of COP allows accurate definition of the pathophysiologic events of pulmonary edema induced by left ventricular failure. Early in the course of pulmonary edema COP increases significantly ($P < 0.001$)[39] (Table IV). This significant increase in plasma COP may be observed in animal models and appears to parallel the increase in left atrial pressure. It is closely followed by an increase in the pulmonary lymph flow with a sharp decrease in its COP from 19.4 to 12.1 ($P < 0.001$).[46] The sequence of events so traced may be summarized as follows: The primary insult, a significant increase in the left ventricular filling pressure, induces a sequence of counterreactions directed at restoration of hemodynamic balance. A colloid-poor fluid passes by ultrafiltration through the lung capillaries, generating a higher COP in plasma that may partly counterbalance the elevated hydrostatic pressure. The lung lymphatic flow subsequently increases, acting as a safety mechanism that protects the lung against fluid accumulation until this mechanism is saturated.

Pulmonary edema may appear in the absence of objective signs of left ventricular failure if hemodilution is present.[47-49] This occurs in animals[2] and man[50] if the COP decreases and the COP–left ventricular filling pressure gradient is diminished by more than 50%. During infusion of colloid-free fluid in patients the direct measurement of COP in addition to the estimation of left ventricular filling pressure may ensure the prevention of iatrogenic noncardiac pulmonary edema.

Microvascular leakage with pulmonary edema may appear in animals in the absence of left ventricular failure or protein depletion.[51,52] A similar syndrome has been reported in man[39] after lung re-expansion and renal transplantation,[53] during bacteremic shock[54] or after heroin or methadone overdoses.[55,56] Awareness of this syndrome and an understanding of its pathophysiology should lead to more rational treatment.[51]

A significant decrease in COP during dilutional cardiopulmonary bypass[37,57,58] has been consistently reported. The postoperative period in these patients is complicated by a decrease in blood volume and an extravascular fluid expansion.[59] The clinical implications of those observations await more comprehensive evaluation before further conclusions can be drawn.

In critically ill patients a significant correlation was found between their lowest measured COP and the final outcome.[35] A COP of 17 mm Hg or higher was found to be safe. When COP decreased to between 16 and 11 mm Hg, survival was in jeopardy. If COP was 10 mm Hg or less the prognosis was poor and the cardiopulmonary failure was likely to be followed by death. Further, if the pressure gradient for microvascular exchanges was taken into account the difference between COP and left ventricular filling pressure was an even better predictor of survival. When the gradient was abolished or was negative, none of 17 patients survived. When the lowest gradient recorded was 9 mm Hg or greater all patients survived. Used as a predictor for survival in critically ill patients, this gradient provided a correct empirical predictor in 87% of the total group of 64 patients, with a theoretical reliability of 82%.[35,60]

Table IV—COP (admission value) in normal ambulatory state and acute pulmonary edema

Condition	COP (mm Hg) Mean ± SD
Normal, ambulatory (n = 19)	25.4 ± 2.3*
Acute pulmonary edema (n = 24)	28.5 ± 3.2*

*Difference significant, $P < 0.001$.

Conclusion

The clinical importance of COP in the regulation of fluid exchange is now clear. Serial determinations of COP can be used as a guide to fluid selection when replacement is required. Measurement of COP enhances assessment of the filling pressure in the left ventricle and provides the clinician with specific and unduplicated information in the differential diagnosis of pulmonary edema. In critically ill patients COP measurement is a reliable predictor of survival.

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